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Immune processes in the pathogenesis of Parkinson's disease – a potential role for microglia and nitric oxide

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Summary

It has been known for many years that immune system alterations occur in Parkinson's disease (PD). Changes in lymphocyte populations in cerebrospinal fluid and blood, immunoglobulin synthesis, and cytokine and acute phase protein production have been observed in patients with PD. In this regard, PD patients exhibit a lower frequency of infections and cancer, suggesting that immune system stimulation may occur. This hypothesis is further supported by the observation of T-cell activation leading to the production of interferon γ in PD. As in other CNS degenerative diseases, in damaged regions in the brains of PD patients, there is evidence of inflammation, characterized by glial reaction (especially microglia), as well as increased expression of HLA-DR antigens, cytokines, and components of complement. These observations suggest that immune system mechanisms are involved in the pathogenesis of neuronal damage in PD. The cellular mechanisms of primary injury in PD have not been clarified, however, but it is likely that mitochondrial mutations, oxidative stress and apoptosis play a role. Furthermore, inflammation initiated by neuronal damage in the striatum and the substantia nigra in PD may aggravate the course of the disease. These observations suggest that treatment with anti-inflammatory drugs may act to slow progression of PD.

key words: inflammation • neurodegeneration • immune system • nitric oxide • dopamine • free radicals

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BACKGROUND

Idiopathic Parkinson's disease (PD) is a degenerative disorder of unknown etiology. Several pathogenic mechanisms have been proposed that lead to degeneration of dopaminergic neurons, such as metabolic factors, oxidative stress and mitochondrial dysfunction. The main anatomic features of brains from PD patients include a diminished number of melanized dopaminergic cells in the substantia nigra (SN) and in related brain stem nuclei, a decrease in the dopamine content in nigrostriatal and mesolimbic pathways, the presence of Lewy bodies, and the deposition of neuromelanin [1,2]. The perturbation of several neurotransmitters and neuropeptides has been reported in PD, indicating a more complicated and widespread pathology.

The cellular mechanisms that lead neuronal cell death in PD are unknown. In addition to the well-studied infections, environmental (toxins) and genetic factors, mitochondrial dysfunction and aggravated oxidative stress are possible causes [3]. Dopamine metabolism increases production of free radicals that may be toxic to dopaminergic cells. Increased lipid peroxidation, a diminished level of reduced glutathione and high levels of iron in the substantia nigra of patients with PD suggest augmented oxygen free radical formation [4]. Additionally, a defect of complex I of the mitochondrial respiratory chain has been detected in PD and confirmed at the biochemical level [5,6]. Analysis of mitochondrial DNA of patients with PD has revealed various missense mutations in mitochondrial complex I genes that may be responsible for its dysfunction and may contribute to the pathogenesis of PD [7,8].

The role of immune mechanisms in neurodegenerative diseases such as PD is an important area of investigation [9]. Death of, or injury to, neurons leads to activation of glia and production of many pro-inflammatory cytokines and molecules. This process resembles classic inflammation, but with minimal or no participation of macrophages and lymphocytes from blood.

LYMPHOCYTES

Invasion of lymphocytes into brain parenchyma is a regular feature of several brain pathologies including viral encephalitis, multiple sclerosis (MS), paraneoplastic syndromes, and to lesser degree in stroke and neurodegeneration [10]. Few T lymphocytes are normally found in healthy CNS; migration of lymphocytes into brain parenchyma is likely limited by the blood-brain barrier. Activation of endothelium and expression of adhesion molecules on endothelial cells and on lymphocytes is necessary for the entry of lymphocytes into the brain. It has been shown that specific activation of lymphocytes against brain antigens is crucial for T-cell accumulation in a lesion but not for access through blood-brain barrier [11]. When recognizing specific antigen, lymphocytes invading the CNS may initiate an inflammatory reaction, but when they do not find a target quickly disappear, likely via apoptosis [12].

In MS, a chronic inflammatory disease of the CNS, the lymphocytic infiltrates contain a preponderance of CD8+ cytotoxic T-cells [10]. This T-cell population usually constitutes the majority of infiltrating lymphocytes, independent of the type of pathology. Cytotoxic T-cells, when activated by binding to MHC class I complex on a host cell, kill infected or transformed cells in a direct manner. These reactions are beneficial if directed against a pathogen but harmful in autoimmune processes or in excess.

In PD, lymphocyte presence in brain has not been described, but they are present in very low numbers in the brain of patients with Alzheimer's disease, amyotrophic lateral sclerosis and traumatic damage. In such pathologies it is unknown if T-cells invading the CNS recognize self-antigens and begin clonal expansion. In culture, it has been shown that cytotoxic lymphocytes may damage axons [13]. In the Rasmussen's syndrome in children, it has been shown that CD8+ T-cells are juxtaposed to MHC class I-expressing neurons, strongly suggesting the involvement of CD8+ T-cells in this brain pathology [14].

Our studies of the mouse MPTP model of PD do demonstrate CD8+ T-cell infiltration, however [15] (Figure 1). The blood-brain barrier is not damaged following MPTP treatment and a lymphocytic infiltration

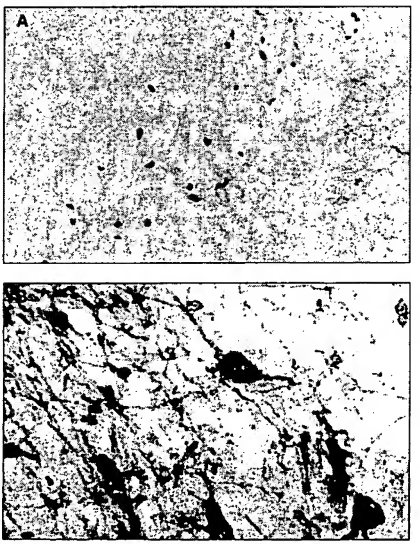

Figure 1. Lymphocytic accumulation in the substantia nigra following MPTP intoxication. [16]
A. T cells are stained for CD4 (black) and CD8 (brown) molecules. Infiltrate contains mainly CD8+ cells. Magn. x 200.
B. CD8+ T cells shown in very close relation to axon of dopaminergic neuron. Magn. x 400

was present in brain parenchyma in striatum and the SN from the first days following treatment with MPTP. Interestingly, we found that peak levels of infiltrating T-cells correlated temporally with the occurrence of the highest level of neuronal damage. Additionally we observed increased MHC class I antigen expression in sites of lymphocytic accumulation [16]. These observations are consistent with the hypothesis that in this model, lymphocytes aggravate dopaminergic cell injury.

Recent research, however, indicates quite the opposite role of lymphocyte accumulation in brain lesions and inflammatory response after CNS injury. It has been shown that autoimmune T lymphocytes, when injected into animals following spinal cord injury [17] or experimentally crushed optic nerve [18], promote long-lasting recovery from the primary insult. Studies suggest that autoreactive T-cells may mediate this protective effect on neurons by secreting neurotrophins, such as BDNF, nerve growth factor (NGF), neurotrophin-3, and neurotrophin-4/5 [19]. It has been shown, furthermore, that antigen stimulation increases production and release of neurotrophins from lymphocytes [20].

CYTOKINE EXPRESSION

Pro-inflammatory cytokines are part of the inflammatory response in the injured brain. They are secreted by immunocompetent cells but also by glia and neurons. Increased expression of pro-inflammatory cytokines, such as interleukin-1 and 6 (IL-1, IL-6), and tumor necrosis factor alpha (TNFα) has been found in cerebrospinal fluid and in brains of patients with PD [21]. Increased levels of IL-2 have also been shown in hippocampus in PD [22]. In the mouse model of MPTP-induced PD, increased levels of mRNA for IL-1β, TNFα, IL-6, IL-10, INFγ in striatum have been observed [23].

IL-1β and TNFα are toxic to dopaminergic neurons in culture, inducing neuronal loss in a NO-independent manner [24]. In addition, these cytokines are especially potent in their ability to stimulate adhesion molecule expression on endothelium, MHC expression on immunocompetent cells, as well as activate microglia and astrocytes. IL-1β and IL-6 augment amyloid precursor protein production and β-amyloid formation and are involved in pathogenesis of Alzheimer's disease [9]. In transgenic mice, overexpression of IL-6 causes encephalopathy with astrogliosis, neuronal loss, demyelinization and edema [25]. TNFα has a well-documented toxic effect on oligodendrocytes and plays an important role in the pathology of allergic encephalomyelitis (EAE) and probably in MS [26]. In addition, polymorphism of TNFα genes correlates with early onset of sporadic PD in Japanese patients [27].

Cytokines may, however, also have a protective effect on neurons. For example, IL-1 amplifies secretion of some neurotrophic factors, such as NGF [28], and activates astrocytes to guide neurite outgrowth of dopaminergic neurons [29]. Additionally, IL-1 together with IL-11, leukemia inhibitory factor (LIF), and GDNF, promotes differentiation of neural progenitor cells into dopaminergic neurons [30]. PD patients homozygotic for allele 1 at position -511 of the IL-1β gene have an earlier onset of the disease than those homozygotic for allele 2, which produces higher amounts of IL-1. Thus higher production of IL-1β might provide some neuroprotective effect for dopaminergic neurons [31]. IL-6 increases dopaminergic neuronal survival in culture and regulates dopamine synthesis [32]. The augmented IL-6 level in cerebrospinal fluid in PD correlates inversely with severity of PD, suggesting that upregulation of IL-6 occurs in order to regenerate lesioned neurons at an early stage of the disease [33]. Which of these two opposing actions of cytokines on neurons occurs (i.e. toxic or protective) may depend on the type of stimuli, the concentration of the secreted molecule, and on receptor expression and interaction. For example, TNFα binding at the type 2 receptor promotes neuroprotection, whereas binding to the type 1 receptor augments neuronal death in retinal ischemia [34].

The presence of neurotrophic factors suggests that the processes of repair and regeneration occur in the SN and striatum of patients with PD. Growth factors may be secreted by activated glia, neurons and even lymphocytes infiltrating brain parenchyma. Epidermal growth factor (EGF), transforming growth factor α and β (TGF), which may inhibit inflammation and exert a direct trophic effect, have been found in striata of PD patients [35]. In an injured striatum, overproduction of GDNF and basic fibroblast growth factor (bFGF) may play a central role in survival and neurite outgrowth [36]. *In vitro*, GDNF diminishes apoptosis of dopaminergic neurons [37] and GDNF treatment of parkinsonic monkeys leads to partial clinical recovery [38]. As bFGF is one of the most important growth factors for dopaminergic neurons, its absence may be involved in PD pathology. In healthy individuals, bFGF is found in large amounts in human brain, especially in the SN and striatum. In PD, bFGF levels decrease significantly, suggesting impaired regeneration [39].

APOPTOSIS

Inflammatory changes (production of toxic radicals by glia, cytokine synthesis), deprivation of growth factors, augmented production of oxygen species, and mitochondrial dysfunction all occur in PD. These factors may trigger neuronal injury, leading to apoptosis. Apoptosis prevents the release of toxic substances (such as proteolytic enzymes) from dying cells, preventing the activation of aggressive inflammation.

Histopathology of PD brains suggests the occurrence of an apoptotic process: cell loss occurs gradually over time (only a few cells per day), and subsequent elimination of cell debris by tissue macrophages (microglia) locally restricts the degenerative process. As examined with TUNEL methods, conventional histologic staining or at the ultrastructural level, however, few, if any, apoptotic cells have been found [40]. In addition, inflammation is present only at relatively low levels, making the identification of the mechanism of cell death more complicated.

Nevertheless, the mitochondrial dysfunction found in PD, in addition to augmented free radical formation and the loss of growth factors, may initiate changes that lead to the slow process of neuronal damage. In addition to the possible trigger factors mentioned above, excess dopamine has also been shown to initiate the process of apoptosis, probably through the formation of free radicals [41].

CHANGES IN THE PERIPHERAL IMMUNE SYSTEM IN PD

It has been observed that patients with PD exhibit changes in their cellular and humoral immune responses. Total lymphocyte count is diminished in patients with PD, and there are phenotypic alterations in circulating peripheral blood lymphocytes. The number of T-cells (CD3+) and B-cells (CD19+) is decreased in PD, especially the CD4+ subset [42,43]. The number of memory helper T-cells is also decreased but to a lesser extent, and the percentage of activated helper T-cells is increased [42]. Lymphocytes from PD patients have reduced proliferative response to mitogens such as phytohemaglutinin and concanavalin A, demonstrating that cellular immune immunity is compromised [44]. Similar observations have been made in animal models of PD, suggesting that the observed immune abnormalities are secondary to dopamine depletion in brain. In rats treated with 6-oxydopamine (6-OXDA) or 1-methyl-4-phenylpyridinium (MPP+) changes in lymphocytic populations have been observed [59]. Mice treated with MPTP show diminished activation of T-cells, decreased IgM production and decreased proliferation of splenic cells [45].

The subpopulation of $\gamma\delta^+$ lymphocytes also plays a role in normal immune responses in infections and in autoimmunity. They have been found to be selectively activated in synovial fluid of patients with rheumatoid arthritis, supporting a role in autoimmune disease. In PD, the $\gamma\delta^+$ lymphocyte population is increased in cerebrospinal fluid [46]. The significance of this finding remains unknown, however. They may be a marker of prior infection or other non-inflammatory disorder. Targets of $\gamma\delta^+$ T- cells may be heat shock proteins (Hsp) that are synthesized in various pathologic conditions, especially infections. An increased ratio of anti-Hsp antibodies has been detected in cerebrospinal fluid but not in sera of PD patients [47]. While these results raise the possibility that the etiology of PD may be infectious, many years of research in this area have yet to uncover the existence of an infectious causative agent. Studies examining the levels of antibodies against various neurotrophic viruses and recognition of viral antigens in brains of patients with PD have failed to identify an infectious etiologic agent [48,49]. In addition, transmission of brain-derived antigens or brain extracts that would contain possible infectious agents from PD brains to animals has also failed to identify an infectious causative agent [50]. It is possible, however, that new or less-well studied pathogens could be involved in PD pathogenesis. Nocardia asteroids, for example, causes locomotor disturbances in mice and intrinsic bodies are found in neurons in brains of affected animals [51].

Influenza A virus is another proposed candidate for the infectious pathogenesis of PD. Influenza A has been shown in experimental models to infect neurons, especially in the SN, cerebellum and hippocampus. Antibodies to influenza A virus in serum of PD patients are not elevated, however, and attempts at finding viral particles in the brain have been unsuccessful. Recent immunochemical studies have revealed, however, the presence of complement and interferon-induced MxA (a GTPase involved in the innate host defense against RNA viruses) in association with Lewy bodies and degenerating neuronal processes [52]. Neurovirulent viruses may be thus responsible for the formation of Lewy bodies and the later death of nigral neurons.

AUTOANTIBODIES

There is some evidence that neurodegenerative process in PD may be aggravated by autoimmune reactions. About 30% of PD patients produce antibodies that bind to neurons in the caudate nucleus [53]. Specific IgG that binds to dopaminergic neurons of the SN has been found in the cerebrospinal fluid of some PD patients [54]and autoantibodies to many neuronal antigens have been found in the serum of patients with PD. These patients also present with skin hypersensivity to such neural antigens as S-100 protein and neuron-specific enolase isolated from brain [55]. Many studies, however, have shown the presence of autoantibodies in serum and cerebrospinal fluid in neurodegenerative disorders including motor neuron disease, Down's syndrome, Huntington's disease, brain atrophy, mental retardation, Alzheimer's disease, schizophrenia, and others. The widespread distribution of autoantibodies in neurological diseases likely indicates a secondary reaction to the release of brain antigen across the blood-brain barrier during the course of the disease. Moreover, autoantibodies have been found to exhibit different specificities (for example against axonal neurofilaments, sympathetic neurons, locus ceruleus) and the incidence of antibodies increases with age [54,55]. The presence of autoantibodies is secondary in PD, but the capacity of autoantibodies to produce demyelinization, alter synaptic connections, disrupt axonal transport, alter protein synthesis, inhibit receptors, increase the permeability of the blood-brain barrier and cause many other dysfunctions has been observed both *in vitro* and *in vivo*. These observations indicate that a humoral autoimmune mechanism may be involved in the progression of PD.

COMPLEMENT CASCADE

Activation of the complement cascade has been identified as an important area of investigation in the pathogenesis of neurodegenerative disorders. The complement system plays a key role in immune reactions and can kill host tissue directly by activation of membrane attack complex (MAC), or indirectly, through activation of macrophages that produce abundant levels of oxygen radicals and other toxic products. In Alzheimer's disease, components of complement have been found in β-amyloid deposits (in both diffuse and senile plaques) and may be involved in β-amyloid formation and neu-

ronal injury. Complement cascade activation and the presence of MAC have also been observed in degenerating neurons in Alzheimer's disease. In PD, components of complement have been demonstrated in Lewy bodies, indicating activation of the classic complement pathway [56]. Moreover, serum from patients with PD has been shown to be toxic to mesencephalic neurons in culture, and this toxicity is mediated by complement activation [57].

In brain, complement may be activated by accumulation of amyloid, extracellular tangles, or Lewy bodies, which apparently act as irritants, additionally initiating reactive changes in microglia and the release of oxygen free radicals and excess glutamate. Thus, secondary complement activation may aggravate tissue damage during neurodegeneration.

GLIAL CELLS: MICROGLIA

Glia constitute the largest group of cells in the brain. Subgroups of glia include microglia, astrocytes and oligodendrocytes. These cell types differ in both origin and function. Astrocytes are the main glial cell type necessary for neuronal survival. They secrete various growth factors, cytokines, and chemokines and eliminate toxins and neurotransmitters. They form the blood-brain barrier (BBB) that maintains the brain environment and divides nervous tissue from the blood stream [58]. Microglia form the tissue macrophage population in the brain and are the main glial cell type that participates in the inflammatory response in brain.

In mammals, glial cells are immunoactive. They are involved with growth and maintenance of neurons and various immune inflammatory-related responses [59]. Cultured astrocytes produce IL-1 [60]. Furthermore, monocytes/macrophages originate in bone marrow and appear to wander in the circulatory system for a short time before settling in various tissues, such as the CNS as resident microglia [61–64]. Microglia exist throughout the brain in the parenchyma, within the microvasculature [65], the choroid plexus and the leptomeninges [61].

Microglial functions and behavior are not well delineated. When cells die in the natural course of CNS development, macrophages can be observed to phagocytize these cells [61]. The macrophage is therefore an immune cell within the brain with the potential to secret neuroactive and signaling molecules that can freely enter/penetrate the blood brain barrier. In the past, we presented a hypothesis showing the potential ramifications of the macrophage's generating 'misinformation' under specific circumstances [66]. This cell may serve as modifier of neurological events and psychological states/conditions [66] and deserves attention as an active component in PD.

An important functional property of mobile immune cells is their migration to sites of inflammation or antigenic challenge. They reach their destinations guided by concentration gradients of specific signal substances (chemotaxis), ensuring that cells migragte to the antigenic challenge. We further propose that chemokinesis, a random non-directed cellular migratory path, also aids in responding to antigenic challenge. For example, once a macrophage arrives at an inflammatory site liberating the chemotaxic stimulus, it must remain there to perform its functions (phagocytosis, nitric oxide [NO] generation, wound debriding etc.) [66]. We hypothesize that chemokinesis ensures macrophage retention through the presence of numerous and highly concentrated signaling molecules at the site of antigenic challenge. Chemotaxis and chemokinesis may, in fact, be the same activity but the immediate environment (low or high levels of one or more signal molecules) dictates which cellular behavior pattern emerges. In addition, normal stimuli that are inappropriately present (due to trauma, nonspecific synthesis and /or release of chemical signals, viral interaction) may initiate either chemotaxis or chemokinesis. Under these abnormal circumstances, however, chemokinesis may be the predominant cellular behavior that emerges due to the nonspecific stimuli and the potential for the macrophage, once activated, to produce numerous secretory products [66]. Under abnormal stimulation it is possible that macrophages, due to nonspecific 'hyperstimulation', are unable to respond to normal antigenic challenge and are thereby 'immunosuppressed' or simply dysfunctional. Interestingly, viral products can induce these cells to become activated, including changing their conformation, thereby generating release of harmful secretory products such as interleukins and NO [67,68]. Given the numerous macrophage secretory products, in this immunosuppressed-hyperstimulated state, this cell may produce such excessive amounts of these products so as to render them toxic [66]. From this position we shall explore the microglia/macrophage's potential to induce tissue damage, i.e. neuronal degeneration, that may translate into PD pathology [66].

GLIAL ACTIVATION IN PARKINSONIAN BRAINS

Both microglia and astrocytes are the source of potentially toxic compounds that may aggravate neuronal injury during degenerative processes such as PD. Astrocytes are generally known, however, for their protective actions towards neurons [58]. They secrete neurotrophic factors such as glial cell-line derived neurotrophic factor (GDNF) and brain- derived neurotrophic factor (BDNF). They contain glutathione peroxidase that prevents the conversion of hydrogen peroxide to hydroxyl radicals. The main enzymes involved in dopamine catabolism, monoamine oxidase-B (MAO-B) and catechol-O-methyltransferase, are expressed by astrocytes, where the majority of dopamine metabolism takes place. Addition of astrocytes to neuronal cultures prevents neuronal death and protects against various toxic compounds [69,70]. In contrast to these protective effects, however, astrocytes may produce pro-inflammatory cytokines and nitric oxide. Astrocytes activated by cytokines express CD23, a protein involved in the induction of NOS and subsequent NO release [71]. Whether NO plays a role in the oxidative stress and neuronal cell death in PD remains to be determined,

however. Indeed, the concentration of nitrites is increased in cerebrospinal fluid and 3-nitro-tyrosine, an index of protein nitrosation induced by peroxynitrite, has been detected in the SN of patients with PD [72,73]. Peroxynitrites, reaction products of nitric oxide and superoxide radicals, are extremely toxic to neurons. Alternatively NO can release iron from ferritin and thus begin the formation of hydroxyl radicals.

Although glial cells may be involved in the pathophysiology of several degenerative diseases, they have been poorly studied in PD. Neuropathological examination in PD generally reveals a mild to moderate astrogliosis that is likely a consequence of neuronal loss and scar formation. Recent evidence supports the possibility that glial cells secrete factors that have either protective or deleterious effects on dopaminergic neurons [74].

The number of activated microglia increases with age in many brain structures including the SN, but their number is even greater in Parkinsonian brains. Furthermore, an augmented number of HLA-DR positive microglia has been described in the SN in PD [75]. In addition to increased expression of MHC, microglia exhibits the morphology of activated cells, suggesting cytokine and other protein production. Additionally, the increased expression of β2-microglobulin, a part of the MHC class I molecule, has been found in microglia in the striatum [76]. It remains to be determined, however, if microglial activation is a consequence of neural degeneration, serving to only phagocytose cell debris, or if it plays a role in aggravating neurodegeneration.

Microglia-derived cytokines influence monoaminergic processes

When considering the role of glia in PD through the generation of tissue damage, it is important to note that microglial signaling molecules can influence catecholamine signaling in the CNS. It has been demonstrated that interleukin-2 (IL-2), which can be induced by microglia, and its receptor are distributed throughout the rat striatum and that IL-2 increases ^{3}H-dopamine release *in vitro* from striatal rat slices [77]. In rat hypothalamus *in vivo*, microglial-derived IL-1 was found to stimulate the release of dopamine and dihydroxyphenyl acetic acid [66]. Palazzolo and Quadri (1990) demonstrated that *in vitro*, IL-1b stimulates the release of both dopamine and norepinephrine from hypothalami of male rats [78]. IL-1 in rat hypothalamus decreased the levels of epinephrine and norepinephrine, and their major metabolite 3-methoxy, 4-hydroxyphenylglycol was elevated [79]. In this study homovanillic acid, a dopamine metabolite, was elevated in the rat striatum, hypothalamus and medulla following cytokine application. Brown and colleagues [80] also noted a stimulatory effect on norepinephrine metabolism by IL-1β in rat CNS.

In mice, IL-1 activates the hypothalamic-pituitary-adrenal axis as well as the cerebral catecholamine metabolism [81]. Interleukin-1 increases the turnover of dopamine in the hypothalamus of lipopolysaccaride (LPS) treated mice [82]. Thus, IL-1- induced activation of the neuroendocrine stress axis persists in LPS-tolerant mice. Cunha [83] demonstrated that IL-8, a molecule also released from activated macrophages, can evoke hyperalgesia in rats by a prostaglandin-independent mechanism. Hyperalgesia can also be evoked in rats by IL-1β [83].

Microglia also have the potential to modify neuroendocrine signal systems. Glial-derived IL-1 can stimulate the release of corticotropin releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus as well as norepinephrine and dopamine release from the hypothalamus [78]. CRH can potentially, in this scenario, stimulate proopiomelanocortin (POMC) release from arcuate nucleus neurons, norepinephrine from the locus ceruleus sympathetic nervous system and glucocorticoid production [84].

It has been shown in culture and *in vivo* that activated microglia can exert deleterious effects on dopaminergic neurons. Interleukin 1 (IL-1), activation of NADPH-oxidase and inducible nitric oxide synthase (iNOS) are the main cytotoxic mediators through which microglia may exert their neurotoxicity. Studies have shown that addition of microglia to dopaminergic neurons in culture increases their vulnerability to toxins and other stress factors [85]. Co-culture of activated microglia and dopaminergic neurons results in increased neuronal death, likely mediated by NO and H_2O_2 release from microglia [86]. Microglial activation by LPS injection to the supranigral area in rat results in neuronal death, which can be partially blocked by inhibiting microglial iNOS [87].

Microglia are very sensitive to any brain insult and react immediately by activation, characterized by morphology change, new surface protein expression and cytokine production. Studies in our lab have shown that in a mouse model of PD rapid microglial activation and secondary astrogliosis occur following peripheral intoxication with 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) (Figure 2 and 3). While MPTP directly injuries dopaminergic cells by disrupting the function of complex I of mitochondria, we have shown, however,

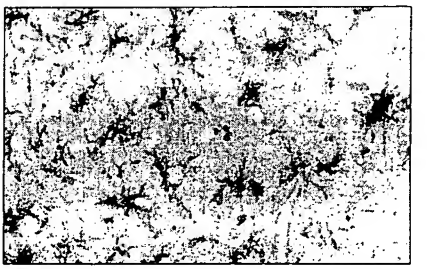

Figure 2. Microglial accumulation in the pars compacta of the substantia nigra following MPTP treatment. Cells stained with anti-MHC class I antibody. Magn. x400.

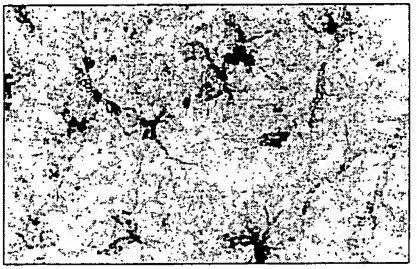

Figure 3. Astrocytes activation in the substantia nigra following MPTP intoxication. Cells are stained with anti glial fibrillary acidic protein antibody (brown) and double stained for IL-6 (black). Magn. x400.

that glial activation precedes neuronal degeneration [88,89]. This indicates that in addition to a direct effect of MPTP, some of the exerted toxicity in this model may be mediated by microglial activation. Additionally, inhibition of microglial function with anti-inflammatory treatment using dexamethasone [16] and indomethacin [90] or with minocycline [91] resulted in greater neuronal survival after MPTP treatment. In summary, microglia have the ability to produce neuroactive cytokines as well as other neuroactive signal molecules (see below) as well as influence catecholamine processes that are critical to Parkinson's pathology, i.e. dopamine. Here, excessive dopamine presence associated with microgial activation may generate free radical formation, hastening dopamine cell degeneration.

Nitric Oxide

Nitric oxide (NO) is an important molecule involved with normal physiological functions as well as processes that have the potential to damage tissues due, in part, to its free radical nature [92–95]. Interestingly, it appears to work as a neurotransmitter [96] as well as an immune cytotoxic substance produced by activated macrophages [97–99].

NO signaling occurs in diverse systems including the immune, cardiovascular and nervous systems [100–105]. NO derived from constitutive nitric oxide synthase (cNOS) may occur in two functional forms: the first present at low 'tonal' or 'basal' levels [106] that can be increased slightly for a short time in response to various biological signals [104]such as actelycholine (ACH). This brief enhanced release of cNOS-derived NO can have profound physiological actions that are evident long after NO levels have returned to the basal level [97]. For example, endothelial cells briefly exposed to morphine produce increased levels of NO as a result of eNOS activation [97]. The increased levels of NO are maximal within 10 minutes and observed for only 10-20 minutes following stimulation. The cells respond to the transient increase in NO levels by changing their shape from elongated to round, a process that takes several hours to occur, and reversion back to the initial conformation is not observed for 18-24 hrs post NO exposure [97].

These data suggest that the capacity for NO production is omnipresent in cell types that express NOS, and that the level of NO production can be regulated rapidly or slowly depending on the organism's needs [106]. The presence of different regulatory processes imply that NO may have different functions in various tissues and that modulation of the level of NO produced may provide a mechanism for induction of divergent activity using the same signal molecule [106].

NO functions as a antibacterial and antiviral agent with the ability to down-regulate proinflammatory events [95,107–114]. Furthermore, given NO's constitutive nature it may also be regarded as part of an innate immune response since it also is found in animals 500 million years divergent from man [106].

We have hypothesized that certain classes of cells are constitutively activated and can respond to microenvironmental changes [2]. This low level of NO production may provide a major pathway to dampen microenvironmental 'noise' that would otherwise nonspecifically and inappropriately lead to increased activation. In this regard, NO may modulate the threshold required for activation of these cells [106] and the magnitude of the subsequent response [115]. A diminished level of NO would then represent a disinhibitory process that results in overcoming the inhibitory influence by changing the level of NO production and the corresponding levels of excitatory signal required for cellular activation [106]. Notable examples of such a process abound in the in the literature. Indeed, exposure of cells to lipopolysaccaride (LPS) triggers an excitatory signal that reduces the constitutive production of NO and activation of these cells then occurs [108,109].

Nitric oxide synthase regulation

Recent data has emerged from the literature demonstrating that NO itself, either exogenously applied or via cNOS stimulation, can attenuate the induction of iNOS in vascular smooth muscle, neutrophils, microglia, astrocytes and hepatocytes [116–122]. In this regard, we have also demonstrated that NO can diminish cNOS-derived NO production in these cell types [123] as well as iNOS-derived NO release [108]. Furthermore, cNOS-derived NO can inhibit iNOS-derived NO induction by inhibiting iNOS expression in human endothelial cells [108,124].

The apparent autoregulatory action of NO has been extended to include the phenomenon that iNOS inducers, such as LPS and IFN can inhibit cNOS via tyrosine phosphorylaton of eNOS [125,126], demonstrating that excessive NO, regardless of the source, can down regulate further NOS activity. In our earlier report, however, we found that cNOS derived NO inhibits iNOS expression only if the cNOS stimulators are present first [108], suggesting the existence of an important regulatory mechanism of physiological significance. In the

absence of cNOS-coupled NO production, proinflammatory signals are capable of iNOS induction with subsequent increased NO release after a 2–4 hr latency period. This allows for a critical immune response / trauma evaluation period to occur and the dependence of NOS on calcium may be a critical step in differentiating the end-intentions of the released NO. Indeed, rapid calcium-cNOS coupling occurs to mediate a rapid response that is of short duration, as is the case for IL-10, morphine, anandamide, endothelin, thrombin and estrogen [106,127,128]. In contrast, iNOS-derived NO must occur after excitation and for a longer time periods to sustain NO's antibacterial, antiviral and down regulating actions following excessive stimulation. This dependence on calcium, therefore, directly regulates the strength of NO's actions to meet specific circumstances.

Reinforcing the concept of NO's critical role in a pathological process and the presence of an autoregulatory mechanism controlling its release is the finding that following exposure of cells to cNOS stimulators and the subsequent NO-dependent down regulation, cells in culture experience a period of hyperactivity [109,115, 129,130]. This same biphasic phenomenon occurs following exposure of various cells from animals divergent in evolution by 500 millions years to cNOS activators or NO donors [109,115,129,130]. We surmise that exogenous NO initially tips the balance favoring a decrease in cell activity and mimics that observed following endogenous cNOS derived NO signaling. Following the initial NO-associated down regulation, the cells rebound into hyperexcitability, as noted earlier. We surmise this is caused by the inhibition of NOS by NO, thus freeing the cells from the basal influence of NO, resulting in activation/excitation. Interestingly, we have speculated that this down regulation followed by a hyperexcitatory phase, for example in immunocytes, is beneficial since it serves to heighten surveillance after the down regulation, leading to the detection of any abnormal activity that occurred during this period [109,115,129,130]. Thus, the presence of the autoregulatory process can even be deduced from this biphasic phenomenon.

Microenvironmental NO production: Parkinson's disease and free radicals

From the earlier discussion it becomes clear that the basal level of NO derived from cNOS may serve as the key modulatory entity regulating a complex cascade of processes associated with maintaining cell health (Figure 4) [106,131]. This process has recently been reviewed for its relevance in Alzheimer's disease [132]. It becomes important, therefore, to determine how a particular microenvironment may alter basal NO level. NO has the potential to interact with oxygen, metals and other free radicals [133]. NO can also form peroxynitrite ($ONOO^-$) and dinitrogen trioxide (N_2O_3), following an interaction with the superoxide radical (O_2^-) and oxygen, respectively [134]. In this regard, NO's direct effect is evident when in low levels and of short duration, such as that occurring under physiological conditions (including the appropriate pH) [134]. For example, NO interaction

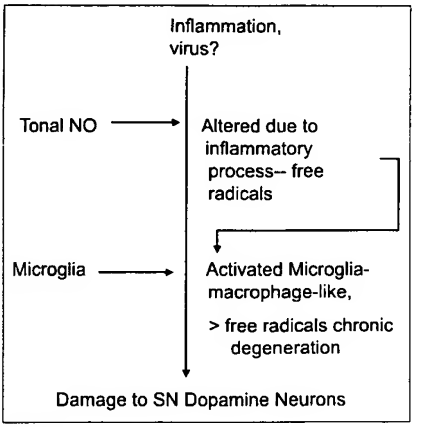

Figure 4.

with the heme proteins represents the activation of soluble guanylyl cyclase (sGC) and/or cyclooxygenase (COX) [135,136,137]. This last interaction is important in the regulation of a proinflammatory process [137]. Additionally, at low NO concentrations (e.g. when it is scavenged) it modulates the redox form of COX, converting the ferrous iron to the ferric active form, acting also as a scavenger of superoxide [134]. NO also has the ability to inhibit lipoxygenase [138]. It can reversibly inhibit the heme moiety of cytochrome P-450, preventing the binding of oxygen to the catalytic sites [139,140]. Interestingly at low NO levels H_2O_2 can be consumed to yield HNO_2 [134, 141], suggesting that H_2O_2 might serve to control NO levels [134]. Indeed activation of monocytes with IFN for 24hr results in the appearance of activated ameboid monocytes but not inactive cells, despite the production of high levels of NO. Indeed, cell activation is abrogated in the presence of catalase or superoxide dismutase, suggesting that H_2O_2 inhibition of NO suppression represents an important regulator of cellular activation [127]. Thus, in the absence of H_2O_2, NO activity may be unregulated whereas in the absence of NO, H_2O_2 may generate tissue damage and disruption in energy metabolism as evident in Alzheimer's Disease [106,131]. In this regard, abnormal constitutive NO levels may initiate microglia cell shape changes 'converting' them into active mobile macrophages due to its direct effect on actin polymerization [106,142]. We speculate that this may simply be due to changes in local basal NO levels that may be intiated by a virus (Influenza A as noted in an earlier discussion) or some form of local trauma or metabolism enhancement at a vulnerable time.

As would be expected based on the earlier discussion, mitochondria represent a NO target since NO is an inhibitor of cytochrome oxidase of the electron transport process [143–148], suggesting a NO role in modulating oxygen utilization [143]. The inhibition of cNOS-

derived NO increases oxygen consumption in many animal species [149–153]. This last fact is critical to our NO hypothesis, concerning alterations in basal NO levels and their significance in Parkinson's disease since its autoregulatory process may be halted (see earlier discussion). Furthermore, a NOS isoform, mtNOS, is present in mitochondria [144,154], suggesting an important modulatory function as well.

Heme proteins (e.g, hemoglobin, cytochromes, etc.) reacting with H_2O_2 result in ferryl cation ($FE^{4+}=O$), a toxic substance [155]. However, once in contact with NO, this compound is reduced ($FE^{3+} + NO_2^-$) [134], demonstrating a NO antioxidant action. NO also has the potential to diminish the formation of OH^-, demonstrating once more an antioxidant action [156]. This scavenging property gives NO a major intracellular and extracellular action against oxidative stress [134, 157–163]. Here again we note that in the absence of NO, these reactive chemical species may cause tissue damage associated with a pathological progression.

Indeed, this process may be an underlying factor in the development and progression of PD. That is, dopamine-associated free radical species may not be 'buffered' by normally present NO basal/tonal levels due to neuronal degeneration or a proinflammatory event that initiated this process, such as consumption of basal NO [164]. In this regard, basal NO production may be overwhelmed by such an event and thus the local microenvironment subjected to damage due to free radical formation that would normally be held in check. This cascading process would damage the tissues if its presence were maintained since the NO-autoregulatory process would not and could not function. It is conceivable that this event occurs in brain areas susceptible to alternation of basal NO production, such as the SN, as discussed earlier. Furthermore, if basal/tonal levels are not present or are masked by NO-scavenging free radicals this may lead to a virtual absence of the molecule in which case the autoregulatory NO-associated process becomes non-functional. Here, any further perturbations to the compromised microenvironment may actually lead to iNOS-derived NO release since cNOS-derived NO release is not measurable, leading to iNOS-NO associated damage, such as neuronal degeneration, paradoxically caused by NO itself, masking the initial condition. Indeed, given this high level of NO and the ability of NO to exert antiviral actions [95], the process would remain while any virus is eliminated. In this regard, Parkinson's disease may represent just a proinflammatory event masked by an over production of NO initiating neuronal damage due to non-functional NO autoregulatory processes [164].

DRUG THERAPY AND PD

Immunological changes in PD, in the periphery and brain, may be partially initiated and modified by drug therapy. Dopaminergic drugs may act directly on the peripheral immune system by binding to specific receptors on lymphocytes. Dopaminergic drugs induce interferon γ (INFγ) production in lymphocytes, which may be responsible for the decreased rate of viral infection and neoplasm seen in PD patients. Dopamine and dopaminergic drugs have been showed to act on dopamine D2 and D3 receptors on lymphocytes, stimulating T-cell adhesion to fibronectin [165]. Amantadine increases the CD4+ T-cell population in PD patients, improving T-cell mediated immunity [166]. Furthermore, the number of binding sites on lymphocytes for dopamine and dopaminergic drugs (i.e. D2 receptor expression) increases during levodopa treatment [167].

The possible harmful effects of anti-parkinsonian drugs on dopaminergic neurons are often discussed. Controversy over the early therapeutic use of levodopa in PD stems from the observation that levodopa increases dopamine metabolism, augmenting production of free radical species in the SN. Dopamine has been shown to initiate apoptosis in neurons *in vitro* and exert toxic effects on various cultured cell lines [41]. Thus, treatment with the dopamine precursor levodopa may exaggerate and augment neuronal damage and elicit inflammatory changes in the SN and striatum, i.e. free radical formation. It has been shown, however, that long-term levodopa treatment (for indications other than PD), at large, cumulative doses, is not toxic to human SN neurons and does not lead to development of the symptoms of PD [168]. Dopaminergic agonists may also modify the pathological process in PD. As a group, they have antioxidant properties *in vivo* and *in vitro*. In cell and animal models they protect against various toxins, including MPTP and 6-hydroxydopamine. Some of these effects may be mediated by direct action on mitochondrial membrane potential and the inhibition of apoptosis [169]. Selegiline, a monoamine oxidase-B (MAO-B) inhibitor, also appears to have neuroprotective properties as it slows progression of PD. Inhibition of MAO-B prevents dopamine metabolism and the subsequent formation of oxygen species. Selegiline has also been shown to increase IL-1β production and decrease TNF-α synthesis in cultured peripheral blood mononuclear cells [170]. The immune alterations caused by selegiline have been suggested to have a neuroprotective effect in PD. Indeed, these agents may mimic NO actions simply by scavenging free radicals or decreasing their formation.

ANTI-INFLAMMATORY TREATMENT

A number of epidemiological studies suggest that those who take anti-inflammatory drugs have a reduced prevalence of Alzheimer's disease, a disease in which inflammatory reactions are believed to be important contributors to neuronal loss [171]. One small clinical trial with indomethacin showed arrest of the disease over a 6-month period [172]. In addition, a long-term prospective study has shown that over 2 year use of non-steroidal anti-inflammatory drugs diminishes risk of Alzheimer's disease [173]. In PD, the role of inflammation in the pathogenesis of the disease is not as clearly understood, and epidemiologic studies have shown little to no effect of non-steroidal anti-inflammatory drugs on the prevalence of PD [171]. This in part may

be due to the progression of the disease at the time of diagnosis and treatment.

Moreover, experimental studies using models of PD are more promising. Studies in our laboratory have shown that dexamethasone used in a very narrow range of doses may have a protective effect on MPTP toxicity to dopaminergic cells [16]. We observed the same effect with indomethacin, where only one of the doses was protective, while lower and higher doses were ineffective or even toxic [90]. It was strongly suggested in a retrospectives study of anti-inflammatory drug use in Alzheimer's disease that small doses of anti-inflammatory drugs are sufficient for decreasing the risk of disease [174]. Regarding inflammatory changes in the degenerating structures in PD, similar to that found in AD and other degenerative processes, we suggest that inflammation is a common mechanism contributing to the pathogenesis of neurodegeneration [164]. Anti-inflammatory drugs may therefore be one of the new approaches for therapy of PD and other neurodegenerative disorders since they may mimic the previously present NO-autoregulatory process, decreasing proinflammation.

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